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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,845	11/19/2003	Ruth A. Gjerset	049146-1001	9478

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,845	GJERSET ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24-29 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-29 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/09 as been entered.

Amended claims 22, 24-29, 31-41 are pending in the present application and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 24-29, 31-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

Independent amended claims 22 and 29 recite the limitation "the gene encoding p14ARF" and "the gene encoding p53" in lines 4-5 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because prior to the limitation, there is no recitation of either a gene encoding p14ARF or a gene encoding p53.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 24-29 and 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (US 5,747,469) in view of either Lu et al. (Cancer Res. 62:1305-1310, 01 March 2002) or Tango et al. (Hum. Gene Ther. 13:1372-1382, 20 July 2002); and Almond et al. (WO 99/47690; Cited previously), Teimann, F. (WO 01/11063) and Mizuguchi et al (Molecular therapy 1:376-382, 2000). ***This is a new ground of rejection.***

Roth et al described recombinant viral vectors such as retrovirus, adenovirus, AAV, HSV, or recombinant CMV vectors or recombinant non-viral vectors in liposomal formulations that express p53; and methods of treating cancers (e.g., benign and metastatic or malignant tumor cells including epithelial tumor cells, lung carcinoma and

breast cancer cells) in a patient by administering the recombinant vectors to cancer cells in combination with chemotherapy or radiation therapy (see at least Summary of the Invention in cols. 3-9; and issued claims).

Roth et al did not teach specifically a method of inducing killing or apoptosis or growth arrest of malignant or metastatic cancer cells, **including p53-positive cancer cells**, by contacting said cells with a bicistronic contruct comprising a single promoter controlling the expression of a sequence encoding p53 and a sequence encoding p14ARF, wherein the sequence encoding p14ARF is located in a first cistron downstream from the promoter and the sequence encoding p53 is located in a second cistron downstream from p14ARF sequence wherein the second cistron is translated from an internal ribosome entry site (IRES) located between the first and second cistrons.

At the effective filing date of the present application (12/17/2002), Lu et al disclosed that **tumors without a p53 mutation often resistant to p53 gene therapy** (see at least the abstract). **Lu et al. disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2 whose expression is induced by p53 but is inhibited by ARF** (page 1307, col. 2 and page 1305, col. 1). Lu et al. showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu et al further taught

that **co-expression of p53 with p14ARF in gene therapy will be more effective for tumors that have p53+ tumor cells** (page 1309, col.1).

Tango et al also disclosed that **co-transfection of human cancer cells both *in vitro* and *in vivo* with recombinant vectors (administered simultaneously) expressing p14ARF (human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy** (see at least the abstract). Tango et al. taught that **p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function**.

None of Lu et al. and Tango et al. taught specifically that both p53 and p14ARF nucleic acid sequences are present in a biscistronic construct and under the expression control of a single promoter.

Also at the effective filing date of the present application, Almond et al described generally a cancer treatment with two or more genes at the same time (the genes could be from the same or different functional groups such as tumor suppressor genes), which augments the action of one or both genes (see at least Summary of the Invention and page 9, lines 18-24). Almond et al taught that **the use of separate vectors, each encoding a different therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity and reduced transduction efficiency , and that the use of separate delivery vectors does not result in the consistent, reproducible expression of both genes in the same target cell** (page 3, lines 11-18). Almond et al

disclosed **that these problems could be reduced by introducing both therapeutic agents, e.g., including a p53 gene, on a single vector such as adenovirus, AAV, herpes virus or retrovirus vector or in a liposome, which ensures that both genes are expressed in the same cell; and the genes may either be present in the vector in separate expression cassettes, e.g., each under control of a different promoter; or they can be present in a single expression cassette under control of the same promoter with an IRES separating the genes** (see pages 4-10 and 84). Almond et al also taught the multi-gene therapy can be combined with radiation therapy or chemotherapy (page 91).

Additionally, Tiemann already described at least **bicistronic viral vectors, e.g., retrovirus or AAV or non-viral vectors for the treatment of malignant or metastatic cancers, e.g., liver, breast, lung, melanoma or prostate, comprising coding sequences for various combinations of tumor suppressor genes, including the combination of p53 and p14ARF, under control of a single promoter and separated by an IRES**; and use of the same (e.g., as a pharmaceutical composition) in treating cancers (see the entire reference, especially, in the translation, at pages 8-12, and claims 1, 3, 17-19 and 22-28). Tiemann also disclosed that treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells (Figure 3). In the exemplified HV-012 recombinant bicistronic vector for tumor gene therapy, **p53 cDNA was cloned in the second cistron of the bicistronic vector** (page 15, first full paragraph and Figure 2).

Moreover, at the effective filing date of the present application Mizuguchi et al also taught that **IRES-dependent second gene expression is significant lower (ranging from 6 to 100% and in most cases between 20 to 50%) than cap-dependent first gene expression in a bicistronic vector** (see at least the abstract).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Roth et al. by also using a recombinant vector co-expressing p14ARF and p53 sequences under the control of a single promoter in the form of a bicistronic expression vector, wherein the p53 sequence is located in a second cistron of the bicistornic expression vector for treating benign and/or metastatic or malignant tumor cells, and particularly for p53-positive cancer cells, in a patient in light of the teachings of either Lu et al. or Tango et al. together with Almond et al., Teimann and Mizuguchi et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because both Lu et al. and Tango et al. taught that co-expression of p14ARF with p53 improved the effectiveness of p53 by blocking the inhibitory effects of MDM2 on p53. Moreover, Tienmann already taught that treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells; and that these two genes can be present in a bicistronic vector construct. Furthermore, Almond et al also taught explicitly that the use of separate vectors, each encoding a different therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity and reduced transduction efficiency, and that the use of separate delivery vectors does not result in the consistent, reproducible expression of both genes in the same target cell.

With respect to the limitation that the p53 sequence is located in a second cistron downstream from the p14ARF sequence in the bicistronic vector construct, an ordinary skilled artisan would have been motivated to carry out this specific modification because **the expression of p14ARF is more important and/or critical relative to the p53 expression, particularly for treating p53 positive cancer cells**, since Lu et al. already disclosed that **a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and Tango et al. also taught that p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function**; coupled with the fact that **IRES-dependent second gene expression is significant lower (ranging from 6 to 100% and in most cases between 20 to 50%) than cap-dependent first gene expression in a bicistronic vector as taught by MIzuguchi et al.**

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Roth et al. with either Lu et al. or Tango et al. and together with Almond et al., Teimann, F. and Mizuguchi et al.; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments **related in part to the above new rejection** in the Amendment filed on 3/02/09 (pages 5-11) along with the Declaration of Dr. Ruth Gjerset filed under 37 C.F.R. 1.132 on 3/2/09 have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. With respect to the issue that the prior art fails to teach or suggest all the claimed elements of the currently amended claims or motivation to combine, particularly with the limitation that the p14ARF sequence be located in a first cistron downstream from the promoter and the p53 sequence be located in a second cistron downstream from the p14ARF sequence in a bicistronic vector construct.

As already noted in the above new ground of rejection, an ordinary skilled artisan would have been motivated to carry out the specific modification to meet the above limitation because **the expression of p14ARF is more important and/or critical relative to the p53 expression, particularly for treating p53 positive cancer cells**, since Lu et al. already disclosed that **a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and Tango et al. also taught that p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function**; coupled with the fact that **IRES-dependent second gene expression is significant lower (ranging from 6 to 100% and in most cases between 20 to 50%) than cap-dependent first gene expression in a bicistronic vector as taught by Mizuguchi et al.**

2. Applicants further argued of surprising and unexpected results using a bicistronic construct with p14ARF in the first cistron and p53 in the second cistron following an IRES element as evidenced by the new Declaration of Dr. Ruth Gjerset filed on 3/2/09. The surprising results are the enhanced translation of the p53 protein compared to the single gene p53 vector or compared to a combination of p14ARF and p53 single gene vectors, and this evidence demonstrates a differential effect of p14ARF on CAP-independent translation versus CAP-dependent translation and to achieve maximal p14ARF and p53 levels in transfected cells. Applicants also argued that this evidence also explains why as shown in previous Declaration that the bicistronic Adp14/p53 vector used (p14ARF-IRES-p53) surprisingly results in 40 times the efficacy of the combination of p14ARF and p53 single gene vectors.

First, it should be noted that the currently amended claims do not require any particular translation level of the p53 sequence in the second cistron of the recited bicistronic vector construct in a method of inducing killing or apoptosis or inducing growth arrest of malignant or metastatic cancer cells.

Second, once again it is also noted that there is nothing unexpected or surprising **regarding to the highly effectiveness of the single promoter p14ARF-IRES-p53 bicistronic vector relative to the dual vector system at killing p53-positive cancer cells (e.g., enhanced killing or apoptosis or enhanced growth arrest) particularly in light at least the teachings of Lu et al, Tango et al., Almond et al, Tiemann and Mizuguchi et al as presented in the above new ground of rejection**. Especially, Almond et al taught explicitly that the use of separate vectors, each encoding a different

therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity and **reduced transduction efficiency**, and that the use of separate delivery vectors does not result in the consistent, reproducible expression of both genes in the same target cell. The exact mechanism (e.g., enhanced translation via the binding of messages to light vs heavy polysomes and/or differential effect of p14ARF on CAP-independent translation versus CAP-dependent translation) that yields the effectiveness or enhanced killing p53-positive cancer cells in the method as claimed is irrelevant.

Third, the examiner notes that the as-filed specification at the filing date (11/19/03), let alone at the effective filing date (12/17/02), fails to teach any concept regarding to the issue that p14ARF suppresses CAP-dependent cellular translation and/or p53 message that is expressed from a second cistron and downstream from an internal IRES of a bicistronic vector is bound preferentially to heavy polysomes (enhanced translation).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633